Side-Chain Kinetic Acidities of 4-Alkyl-1-methylpyridinium Ions. Opposing Resonance and Charge Neutralization Effects on Reactivity

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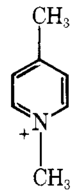
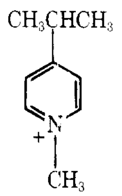
Hydrogen–deuterium exchange of the methyl and methine protons of 1,4-dimethylpyridinium and 4-isopropyl-1-methylpyridinium ions at 75 °C in D_2O is subject to general base catalysis with Brønsted coefficients of 0.74 and 0.72, respectively. Steric hindrance is encountered with 2,6-dimethylpyridine bases; lyate ion is about 10^2 less reactive than predicted by the Brønsted correlation. The isopropyl is 7.3 times less reactive than the methyl carbon acid when lyate ion is the catalyst. This difference in reactivity decreases as the basicity of the catalyst decreases, being a factor of 2.0 toward acetate ion, the weakest base examined. The transition state for deprotonation is believed to be pyramidal, having considerable delocalization of charge from the chain into the ring. Comparisons with nonaromatic ammonium ions reveal the effect of a reduction in resonance energy in a transition state on reactivity, and the extent to which this is offset by charge neutralization.

Nonaromatic ions having a quaternized nitrogen atom have played an important role in developing an understanding of the effects which influence the acidity of carbon acids.[1,2] By contrast, little quantitative information is available concerning the acidities of aromatic ions containing a similar quaternized site. We report the results of a study involving the kinetic acidities of pyridinium ions which undergo deprotonation at the carbon side chain bonded to position 4. Comparison of results for the nonaromatic ions with our new data provides a most revealing glimpse into the interplay of resonance and charge neutralization effects which dominate the reactivity of the heteroaromatic carbon acids.

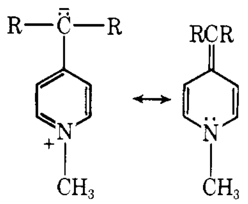
We have determined the kinetic acidities of 1,4-dimethyl- (I) and 1-methyl-4-isopropylpyridinium ion (II) carbon acids which give conjugate bases III (R = H and CH_3) on deprotonation. Particularly instructive is a comparison of the reactivities of I and II with those of tetramethylammonium ion (IV) which gives ylide V on proton removal[1] and with 1,1-dimethyl-1,2-dihydropyridinium ion (VI).[2] The reactivity of a methyl group of IV is essentially determined by the inductive and electrostatic effects of the adjacent positively charged site; a charge localized ylidic intermediate forms when a proton is eliminated. Nonaromatic ion VI gives anionically delocalized ylide VII on proton loss; charge delocalization constitutes an additional factor enhancing the reactivity of VI.



I



II



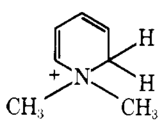
III

$\overset{+}{CH_3N}(CH_3)_3$

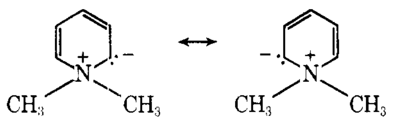
IV

$\overset{-}{C}H_2\overset{+}{N}(CH_3)_3$

V



VI



VII

Deprotonation of I and II is expected to be influenced by similar inductive, electrostatic, and charge delocalization effects. However, two different and important effects operate when III is produced: (a) charge neutralization occurs, providing additional stabilization not available to bases V and VII, and (b) a reduction in resonance delocalization energy impedes proton removal. The comparisons provide considerable insight into the acidities of other positively charged heteroaromatic carbon acids as well as of I and II.

Results

Rate constants for deprotonation of the 4-methyl protons of I and the methine proton of II in D_2O at 1.0 M ionic strength were obtained using an NMR method of analysis. Deprotonation is catalyzed by OD^- and by buffer bases; i.e., deprotonation is subject to general base catalysis. The deuteration of I in NaOD–D_2O[3] and in CH_3OD[4] has been reported.

Isotope exchange was observed when a saturated solution of $Ca(OD)_2$ was employed as the catalyzing base. Pseudo-first-order rate constants, k_ψ, were obtained at several temperatures (Table I). In the case of I, hydrogen isotope exchange proceeded too rapidly at 75 °C, and with II it proceeded too slowly at 25 °C for convenient study; convenient rates were found for both compounds at 50 °C.

Several buffers were employed as catalysts at 75 °C. Under these conditions deprotonation is brought about by the action of both the buffer base and deuteroxide ion; i.e., k_ψ is given by eq 1 where B is the buffer base, k_{OD} and k_B are second-order rate constants associated with catalysts OD^- and B, respectively, and K_a is the dissociation constant of buffer acid.

$$k_\psi = k_{OD}[OD^-] + k_B[B]_{tot}\frac{K_a}{[D^+] + K_a} \qquad (1)$$

The contribution of lyate ion to the total observed rate constant is sufficiently large using phenol and 4-amino-2,6-dimethylpyridine buffers in the case of I so that an accurate value can be obtained for k_{OD}. The values 0.438 and 0.475 $M^{-1}\,s^{-1}$ derived with these two buffers, respectively, are in good agreement. Only the former buffer was examined with II, giving a k_{OD} value of $5.86 \times 10^{-2}\ M^{-1}\,s^{-1}$ which is in reasonable agreement with the value 6.55×10^{-2} obtained using calcium deuteroxide.

These k_{OD} rate constants obtained at several temperatures give rise to the enthalpies of activation, $\Delta H^{\ddagger}$, for I and II, 15.6 and 17.8 kcal/mol, respectively, and entropies, $\Delta S^{\ddagger}$, of −15.5 and −13.2 cal/deg-mol, respectively. The rate constant calculated for II at 25 °C with these values is $6.93 \times 10^{-4}\ M^{-1}\,s^{-1}$.

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Table I. Conditions and Results for the Hydrogen–Deuterium Exchange of 1,4-Dimethylpyridinium Iodide (I) and 1-Methyl-4-isopropylpyridinium Iodide (II) in D_2O at 1.0 M Ionic Strength and 75.0 °C

Substrate	Buffer	pK_a[a]	pD[a]	Total buffer, M	k_ψ, s^{-1}	k,[b] $M^{-1} s^{-1}$	k_B^{Me}/k_B^{Pr}
I	$Ca(OD)_2$		12.24[c]	Satd	9.93×10^{-4}[c]	7.30×10^{-2}[c]	7.34[e]
			12.98[d]	Satd	1.15×10^{-4}[d]	8.68×10^{-3}[d]	
II	$Ca(OD)_2$		11.60	Satd	7.80×10^{-4}	6.55×10^{-2}	
			12.27[c]	Satd	1.16×10^{-4}[c]	7.78×10^{-3}[c]	
I	Phenol	9.99	8.89	0.0204	2.36×10^{-5}	1.27×10^{-2}	3.26
			9.00	0.0202	3.83×10^{-5}	4.38×10^{-1} (OD^-)	
			9.02	0.102	1.37×10^{-4}		
			10.11	0.0147	3.60×10^{-4}		
			10.35	0.0437	6.36×10^{-4}		
II	Phenol	9.99	9.34	0.0545	3.83×10^{-5}	3.90×10^{-3}	
			9.43	0.102	9.50×10^{-5}	5.86×10^{-2} (OD^-)	
			9.89	0.109	1.88×10^{-4}		
			10.37	0.0147	8.37×10^{-5}		
			10.40	0.0436	1.64×10^{-4}		
			10.91	0.0600	4.68×10^{-4}		
			11.09	0.0600	4.30×10^{-4}		
I	4-Amino-2,6-dimethylpyridine	9.50	9.11	0.0511	3.10×10^{-5}	8.05×10^{-4}	
			9.43	0.102	7.42×10^{-5}	4.75×10^{-1} (OD^-)	
			9.63	0.102	1.07×10^{-4}		
			10.50	0.109	5.21×10^{-4}		
I and II	4-Aminopyridine	8.44	9.42	0.200	1.36×10^{-4} (I)	5.50×10^{-4} (I)	2.42
					4.88×10^{-5} (II)	2.27×10^{-4} (II)	
			9.46	0.220	1.36×10^{-4} (I)		
					4.80×10^{-5} (II)		
I and II	Imidazole	6.68	6.65	0.200	2.20×10^{-6} (I)	2.37×10^{-5} (I)	1.20
					1.72×10^{-6} (II)	1.97×10^{-5} (II)	
			7.73	0.228	6.12×10^{-6} (I)		
					4.70×10^{-6} (II)		
II	2,6-Dimethylpyridine	6.50	6.49	0.202	3.19×10^{-8}	2.58×10^{-7}	
I	Pyridine	5.37	6.45	0.206	9.63×10^{-7}	4.96×10^{-6}	
I and II	Acetic acid	5.25	6.27	0.220	7.06×10^{-7} (I)	3.39×10^{-6}	1.97
					3.51×10^{-7} (II)	1.72×10^{-6}	

[a] Measured at 75 °C. [b] For buffer base and/or OD^- as indicated. [c] 50.0 °C. [d] 25.0 °C. [e] For OD^- base.

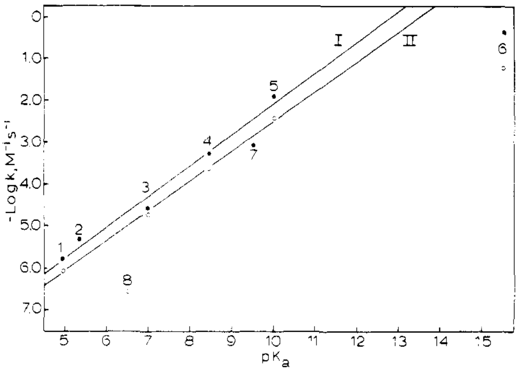


Figure 1. Brønsted plots for the deprotonation of I and II in D_2O at 75.0 °C and 1.0 M ionic strength. Bases include: (1) acetate ion, (2) pyridine, (3) imidazole, (4) 4-aminopyridine, (5) phenolate ion, (6) deuteroxide ion, (7) 4-amino-2,6-dimethylpyridine, and (8) 2,6-dimethylpyridine. Statistical corrections have been made.

In order to obtain a more extensive comparison of the reactivities of I and II and to construct a Brønsted plot the kinetic effects of several other buffers were examined. They include 4-aminopyridine, imidazole, 2,6-dimethylpyridine, pyridine, and acetic acid. Because the reactivities of both substrates are so similar it was convenient at times to examine both in the same mixture. Overlap of the signals for the methyl group of I and the methyl protons of 2,6-dimethylpyridine prevented an analysis of the reactivity of I with this base.

The results obtained at 75 °C summarized in Table I indicate that I and II have very similar reactivities under all the conditions examined. Thus, toward deuteroxide, ion I is only 7.3 times more reactive than II; this relative reactivity, given as k_B^{Me}/k_B^{Pr} in Table I, decreases for the other bases. Toward phenoxide ion, 4-aminopyridine, imidazole, and acetate ion it is 3.3, 2.4, 1.2, and 2.0, respectively. With the exception of the value for imidazole there appears to be a trend suggesting that relative kinetic carbon acidity decreases as the basicity of the catalyzing base decreases. These results may also be expressed in terms of a linear free energy relationship, eq 2

$$\log k_B^{Me} = 1.14 \log k_B^{Pr} - 0.92 \qquad (2)$$

(correlation coeefficient, r = 0.997), which shows that I undergoes slightly larger changes in reactivity than II as basicity is varied. Although these results are interesting because they run counter to the idea that selectivity decreases as reactivity increases, the variations are not large. By comparison, a similar but larger change in relative reactivity was reported for the rates of deprotonation of nitromethane and 2-nitropropane. Here relative reactivity decreased from a factor of 29 toward hydroxide ion to about a factor of 2–4 toward acetate and chloroacetate ions.[5,6]

The range in the second-order rate constant from the least (acetate ion) to the most basic (lyate ion) catalyst is a factor of 1.3×10^5 for I and 3.6×10^4 for II. The reactivity of each substrate toward the catalysts may be expressed in terms of a Brønsted plot. Such a plot is shown in Figure 1. Statistical corrections have been made for the number of acidic and basic sites in a buffer.[7] Acetate ion, pyridine, and phenoxide ion bases all appear to fall on a common line. However, points associated with 2,6-dimethyl- and 4-amino-2,6-dimethylpyridine and also deuteroxide ion all lie below the line generated by the other bases. Eliminating these deviant points gives rise to Brønsted lines described by eq 3 and 4.

$$\log k_B{}^{Me} = 0.74pK_a - 9.49 \qquad (r = 0.991) \qquad (3)$$

$$\log k_B{}^{Pr} = 0.72pK_a - 9.71 \qquad (r = 0.9994) \qquad (4)$$

Deuteroxide ion is 230 times less reactive toward I than predicted by the linear relationship; for II the factor is 500. Such negative deviations for lyate ion are not uncommon; they are believed to reflect the absence of a hydrogen bond between this base and the carbon acid and the energetic cost to bring about partial desolvation of the base in the course of proton transfer.[8]

No doubt the deviations associated with the substituted pyridines reflect steric hindrance to general base catalysis. The deviation is greater where the hindrance is larger, a factor of 39 for the isopropyl substrate and a factor of 4.7 for the methyl compound. The rate retarding factor of 39 is greater, for example, than the value of 5[9] reported for 2-nitropropane but less than the factor of about 150 recorded for isobutyraldehyde-2-*d* and the same base.[10]

The NMR spectrum of the conjugate base of II could easily be recorded in liquid ammonia but that from I was time dependent, suggesting decomposition. Others have demonstrated that the conjugate base of I is unstable.[11] Interestingly, the signal for a methyl group of II shifts downfield by about 15 Hz on deprotonation, suggesting the formation of an allylic proton. Moreover, the extent of deprotonation of I and II by ammonia is not unlike that of nitromethane under similar conditions.[12] The results suggest that these carbon acids have similar ionization constants in ammonia, unlike the very large difference which exists in aqueous solution. The pK_a of I in water is 20.25[13] and that of nitromethane under similar conditions is 10.22.[14] This constitutes additional dramatic evidence that relative acidities may be highly dependent on solvent.[15]

Discussion

Before considering a comparison of kinetic carbon acidities, the nature of the transition states in the deprotonation reactions will be examined. Comparisons of kinetic acidities are most informative when transition states closely resemble products because structural effects on rates are magnified. The transition states for the deprotonation of IV and VI are believed to be product-like, i.e., resemble ylide intermediate.[2]

Nature of Transition States. Both the small kinetic effect of methyl substitution on I to give II and the large Brønsted β value suggest product-like transition states. The transition states probably have a pyramidal geometry at the reacting carbon.[16] Considerable charge is delocalized from the side chain into the ring giving rise to a partial exocyclic double bond.

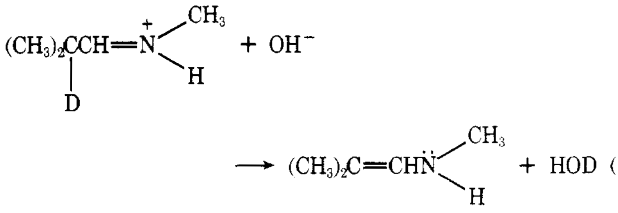
Methyl substitution can be an effective way to probe the hybridization and charge density of a carbanion. When a carbanion has sp^3 or sp^2 hybridization with considerable charge localized on the carbon atom, a methyl substitutent, relative to hydrogen, may exert an electron releasing effect which destabilizes the anion in solution.[20] But a change from an sp^3 to an sp^2 hybridization results in an increase in the strength of the carbon–methyl bond. Depending on the amount of charge on the sp^2 hybridized carbon, either one of the two opposing effects may predominate.[22,23]

The difference in reactivity between I and II ranks among the smallest observed for proton transfer involving related methyl and isopropyl carbon acids. This difference which varies from a factor of 1.2 to 7.3, depending on the catalyzing base, is smaller, for example, than the factor of 29[5,6] found for the deprotonation of nitroalkanes by hydroxide ion where the geometry of the transition state is believed to be pyramidal with a great deal of charge localized at the reactive site.[24,25] Moreover, the difference is markedly less than the factor of 10^4 found for similarly substituted sulfones[26] and sulfides.[27] The small rate retarding effect of the two methyl groups in II reflects the approximate balance between charge destabilization and double bond stabilization in a transition state leading to III.

Although Brønsted β values need to be considered cautiously in attempting to derive information about the extent of proton transfer,[28–31] our large value of 0.7 is consistent with a high degree of transfer. This value is considerably larger than the value of 0.5 recorded for the deprotonation of nitroalkanes by amines[32] but less than the value of 0.9 for the deprotonation of acetone, a carbon acid having a pK_a value similar to that of I.[33]

Reactivity Comparisons. At 75 °C, I and II are about 10^8 times more reactive toward OD$^-$ than IV.[1] This enormous difference is best rationalized in terms of transition states for I and II having considerable delocalization of charge from the side chain into the ring. The reactivity of I serves as a model illustrating the importance of inductive and electrostatic effects free of resonance.

The reactivities of I and II are less than that of VI in the presence of OD$^-$, having rate constants smaller by factors of 8.2 and 61 at 75 °C,[2] respectively. In transition states and conjugate bases formed from these three acids extensive charge delocalization occurs, but only in the case of base III is charge neutralization possible. Such charge neutralization if it were unopposed by another major effect would enhance greatly the kinetic and equilibrium acidities of I and II over VI. An indication of how effective charge neutralization may be in enhancing kinetic acidities is found in a comparison of the reactivity of IV with that of an iminium ion formed from isobutyraldehyde-2-*d*, eq 5. This iminium ion is roughly 10^{13} times (35 °C) more reactive than IV.[10,34,35]



$$(CH_3)_2C(D)H{=}\overset{+}{N}(CH_3)H + OH^- \longrightarrow (CH_3)_2C{=}CH\ddot{N}(CH_3)H + HOD \qquad (5)$$

Another factor must be included in a consideration of the reactivities of I and II. Both of these acids on deprotonation undergo a very large reduction in resonance delocalization energy. Estimates place the magnitude of this thermodynamic barrier for the conversion of I to III at 19.5 ± 4 kcal/mol.[36] Naturally, the change would be somewhat smaller when a transition state rather than intermediate III is formed. Such a very large energy barrier opposes and partially cancels the large beneficial effect associated with charge neutralization. Were it not for the thermodynamic barrier the kinetic and equilibrium acidities of I and II would be vastly greater. A similar conclusion is likely to hold for the great number of heteroaromatic ions related to I and II.

Experimental Section

Nuclear magnetic resonance spectra were recorded on a Varian Associates Model A-60A instrument. Measurements of pD were made on a Beckman Model 1019 Research pH meter equipped with a Corning (476050) semimicro combination electrode.

Chemicals. All common laboratory chemicals, unless specified to the contrary, were reagent grade. Deuterium oxide (99.8%) was obtained from Columbia Organic Chemicals. Stock solutions of DCl were prepared by diluting concentrated HCl with D_2O and standarized by potentiometric titration. Stock solutions of KOD were prepared by dissolving KOH in D_2O; solutions were standardized by potentiometric titration using primary standard grade potassium hydrogen phthalate.

Mallinckrodt sodium acetate was used directly. Pyridine obtained from Mallinckrodt Chemical Works and 2,6-dimethylpyridine from Eastman Organic Chemicals were dried over sodium and distilled from zinc powder. Imidazole from Matheson Coleman and Bell was recrystallized from hexane. 4-Aminopyridine from Reilly Tar and Chemical Corp. was purified by vacuum sublimation and recrystallized from benzene (mp 157–160 °C; lit.[37] 158 °C). The method of Evans and Brown[38] was used to prepare 4-amino-2,6-dimethylpyridine which was purified by successive vacuum sublimations (mp 190–191 °C; lit.[38] 191–192 °C). The purification of phenol was accomplished by adding benzene to phenol, liquified reagent, obtained from Matheson Coleman and Bell, and distilling. Calcium hydroxide was prepared by heating well-washed calcium carbonate in a platinum crucible at approximately 1000 °C with a burner for 1-h intervals until a constant weight was obtained.[39] The freshly prepared oxide was then slowly added to water and the solution was heated to boiling, cooled, and filtered. The solid was then oven dried and crushed to a finely granular state. Calcium deuteroxide was prepared by dissolving calcium hydroxide in D_2O. 1,4-Dimethylpyridinium iodide was prepared from 4-methylpyridine and methyl iodide, mp 153–154 °C (lit.[40] mp 153–153.8 °C).

4-Isopropyl-1-methylpyridinium iodide. Liquid 4-isopropylpyridine (K and K Laboratories) was fractionally distilled; the portion distilling at 181–182 °C was collected. The distillate was then dissolved in methanol and heated at reflux with methyl iodide. After cooling and evaporation to dryness, the crude salt was dissolved in excess ethanol at room temperature. Crystallization was induced by slowly adding small portions of ethyl ether, mp 125.5–128.5 °C (lit.[40] 117–120 °C dec).

Anal. Calcd for $C_9H_{14}NI$: C, 41.08; H, 5.36; N, 5.32; I, 48.23. Found: C, 41.09; H, 5.38; N, 5.28; I, 48.24.

Preparation of Reaction Mixtures. Substrate was weighted along with a corresponding molar amount of internal standard in a 30- or 10-mL volumetric flask. A weighed amount of buffer and/or a known volume of stock solution was added with a Hamilton microliter syringe. In the case of 4-amino-2,6-dimethylpyridine a stock solution of this buffer in D_2O–DCl was employed. Ionic strength was maintained at 1.0 M using KCl.

Kinetic Procedure for H–D Exchange. Kinetics were obtained by two methods. The first method, by which a majority of the work was done, involved the preparation of 3 mL of solution. Approximately 1 mL of this solution was transferred to an NMR tube whch was then flushed with nitrogen and sealed. The remainder of solution was stored under nitrogen for later comparison and pD measurements. A ^1H NMR spectrum was recorded and the NMR tube was then immersed in a constant-temperature bath set at the desired temperature using a National Bureau of Standards certified thermometer. Periodically, the NMR tube was removed and quenched in ice water, and the ^1H NMR spectrum was recorded.

In mixtures with a high deuteroxide concentration, a second method was employed. From 10 mL of stock solution, a 2-mL aliquot was stored under nitrogen for pD measurements. The remaining solution in a 10-mL volumetric flask fitted with a rubber septum was immersed in the bath. Periodically, 0.9 mL of solution was withdrawn and injected into a test tube containing 0.1 mL of a 1.2 M DCl quench solution. The NMR spectrum of this neutralized solution was recorded.

Reactions were followed a minimum of 1.5 half-lives by measuring the change in the integrated area of the NMR signal of the proton(s) of interest with respect to that of a nonexchanging proton in the reaction mixture. The integrals of proton signals were measured in a minimum of five successive sweeps and the average value was taken. Substrate concentrations were 0.40 to 0.45 M.

Usually an internal standard external to the substrate was used. For runs involving the 1,4-dimethylpyridinium iodide, tetramethylammonium bromide was added as an internal standard. In a few instances both substrates were present in the same mixture and so it was necessary, due to peak overlap, to change to sodium acetate as an internal standard. Although acetate ion promotes exchange, it does so slowly. Once a rate constant was obtained for acetate ion, its contribution to the rate could be easily calculated out of the total rate. Catalysis by acetate ion internal standard was significant only in the case of imidazole buffer where it made a contribution to the total rate of ≤12%. In the case of 2,6-dimethylpyridine acting as buffer it was necessary to use the ring protons of the substrate as an internal standard since catalysis by acetate ion was greater than by 2,6-dimethylpyridine. In the case of $Ca(OD)_2$ a small amount of this solid was present to avoid supersaturation and to maintain a constant concentration of base in solution.

From each kinetic run a plot was made of the quantity log $(A/A_{std})_t$ vs. time where $(A/A_{std})_t$ is the ratio of the integrated area of the reacting proton(s) to the area of the internal standard at time t. A pseudo-first-order rate constant, k_ψ, was then calculated from each plot constructed by visually fitting the best straight line through the points.

pD Measurements. Standardization buffers were prepared as recommended by Bates.[41] Prior to measurements at 50.0 and 75.0 °C, the electrode was thermally equilibrated for at least 20 min in 4 M KCl. By rinsing and storing the electrode in solutions maintained at the desired temperature, the electrode was not allowed to cool.

Since the pH meter was standardized and linearized with proteo buffers, it is necessary to add a correction to the meter readings to arrive at accurate pD values. For pD measurements at 25 °C, the pD value is obtained by adding 0.41 to the meter reading.[42] For pD measurements at 75 °C, this factor is 0.35.[43] At 50 °C, a value of 0.38 is obtained by simple interpolation. The apparent activity of deuteroxide ion was calculated using the relationship $pOD = pK_w^D - pD$. The values used for pK_w^D, the dissociation constant for deuterium oxide, are 14.869 (25 °C), 14.103 (50 °C), and 13.526 (75 °C);[44] they are not corrected for small salt effects.[45]

The pK_a of a buffer was calculated from the measured pD at 75 °C and the known buffer ratio for reaction mixtures containing substrate. Considerable scatter was found for phenol buffers. Twelve determinations gave a value of 9.97 with a standard deviation of 0.23. Repeated measurements of four solutions of phenol buffer of the same ionic strength but without substrate gave a pK_a of 9.99 with a standard deviation of 0.09. The latter value was taken as the pK_a.

As the electrolyte solution in the reference electrode contains silver ion, a precipitate of AgI forms in the porous frit at the liquid function, resulting in drifts in pD measurements. Elimination of this drift was accomplished by washing the electrode with thiosulfate solution.

Control Runs. Although the presence of an internal standard, agreement of pD measurements on original and recovered solutions, and the linearity of the pseudo-first-order kinetic plots indicated the absence of important complicating factors, control runs were carried out to determine the stability of both the 4-methyl- and 4-isopropylpyridinium iodides under various conditions.

The two pyridinium iodides were first dissolved in 0.10 M DCl solutions with an acetic acid internal standard and heated at 75 °C to determine their stability and, if possible, measure any exchange catalyzed by D_2O acting as the buffer base. No exchange, as evidenced by the broadening of the 4-methyl singlet or the emerging of a singlet between the 4-isopropyl *gem*-dimethyl doublet, could be detected in the NMR after heating for several days. These NMR spectral changes are a more sensitive indication of initial deuterium substitution than change in the integral ratios.

The same solutions were heated again until the change in the NMR area ratios of substrate to internal standard reached 10%. A precipitate formed but there were none of the above-mentioned spectral changes indicative of isotope exchange. The change in the integral ratio is, therefore, attributed to degradation of substrate. For the 4-methyl compound, heating for a period of 7 days produced the 10% degradation while for the 4-isopropyl compound, heating for a period of 14 days was required to produce this same percent change.

Proteo control runs were then carried out at 75 °C to verify the stability of the two pyridinium iodides in basic solution. The compositions of previously used buffer solutions were duplicated using H_2O in place of D_2O and the mixtures were heated for the equivalent of ten half-lives. For each buffer, the most basic conditions employed in the kinetic study were the conditions duplicated for the control runs. Although kinetic runs were not carried out with the 4-isopropyl compound in 4-amino-2,6-dimethylpyridine buffer, a control run was made using this buffer. Using calcium hydroxide, I was heated for 20 min and II for 140 min. With 4-amino-2,6-dimethylpyridine, I was heated for 220 min and II for 2000 min. In all cases the change in pH (measured at 25 °C) between heated and unheated samples was ≤0.04. Degradation of substrate as measured by loss of the signal for the 4-alkyl group relative to the signal of acetate ion internal standard was less than 10% in all cases.

NMR Spectra of the Conjugate Bases of 1-Methyl-4-Substituted Pyridinium Iodides in Ammonia. To either 1,4-dimethylpyridinium iodide or 1-methyl-4-isopropylpyridinium iodide and benzene internal standard in an NMR tube was added about 1 mL of ammonia. The tubes were sealed and spectra were recorded at probe temperature, about 30 °C. The solution of the 4-methyl compound was opaque and dark green; only the spectrum of starting material was evident, even a day later. The solution of the 4-isopropyl compound was a clear orange; its NMR spectrum consisted of that due to starting material and conjugate base, estimated by integration to constitute about 10% of the mixture.

The experiments were repeated but this time powdered KOH was added as well. The spectrum of the dark green solution of the 4-methyl substrate at −35 °C showed that approximately 20% had been converted to conjugate base. Warming this solution to probe temperature resulted in an increase in the amount of conjugate base but the material appeared to be unstable as the signals slowly disappeared. Only the ring proton signals could be readily characterized: H-3,5, δ 5.55 and H-2,6, δ 6.22, taking benzene as δ 7.40.

Similarly, in the presence of KOH the 4-isopropyl carbon acid at −35 °C gave 30% conjugate base; only conjugate base was observed at probe temperature. The spectrum of the clear orange solution was unchanged after standing overnight: CH_3, δ 1.55, NCH_3, 2.93, H-3,5, 5.37 and H-2,6, 6.02. This spectrum is similar to that reported for 1-carbethoxy-4-isopropylidene-1,4-dihydropyridine in carbon tetrachloride.[46]

Registry No.—I, 2301-80-6; II, 18136-37-3; 4-isopropylpyridine, 696-30-0; deuterium, 16873-17-9.

References and Notes

(1) W. von E. Doering and A. K. Hoffmann, *J. Am. Chem. Soc.*, **77**, 521 (1955).
(2) M. Saunders and E. H. Gold, *J. Am. Chem. Soc.*, **88**, 3376 (1966).
(3) Y. Kawazoe, M. Ohnishi, and Y. Yoshioka, *Chem. Pharm. Bull.*, **15**, 1255 (1967).
(4) N. N. Zatsepina, A. V. Kirova, and I. F. Tupitsyn, *Reakt. Sposobn. Org. Soedin.*, **5**, 70 (1968); N. N. Zatsepina, I. F. Tupitsyn, and L. S. Efros, *Zh. Obshch. Khim.*, **34**, 4065 (1964).
(5) R. P. Bell and D. M. Goodall, *Proc. R. Soc. London, Ser. A*, **294**, 273 (1966).
(6) A statistical correction has been applied to reflect the three equivalent protons of the reactive methyl group.
(7) R. P. Bell and P. G. Evans, *Proc. R. Soc. London, Ser. A*, **291**, 297 (1966).
(8) A. J. Kresge, *Chem. Soc., Rev.*, **2**, 475 (1973); A. J. Kresge and A. C. Lin, *J. Chem. Soc., Chem. Commun.*, 761 (1973).
(9) E. S. Lewis and L. H. Funderburk, *J. Am. Chem. Soc.*, **89**, 2322 (1967).
(10) J. Hine, J. G. Houston, J. H. Jensen, and J. Mulders, *J. Am. Chem. Soc.*, **87**, 5050 (1965).
(11) W. Schneider, K. Gaertner, and A. Jordan, *Ber.*, **57**, 522 (1924).
(12) J. A. Zoltewicz and J. K. O'Halloran, *J. Org. Chem.*, **39**, 89 (1974).
(13) R. A. Cox, R. Stewart, M. J. Cook, A. R. Katritzky, and R. D. Tack, *Can. J. Chem.*, **54**, 900 (1976).
(14) R. G. Pearson and R. L. Dillon, *J. Am. Chem. Soc.*, **75**, 2439 (1953).
(15) C. D. Ritchie in "Solute-Solvent Interactions", J. F. Coetzee and C. D. Ritchie, Ed., Marcel Dekker, New York, N.Y., 1969, Chapter 4; W. S. Matthews, J. E. Bares, J. F. Bartmess, F. G. Bordwell, F. J. Cornforth, G. E. Drucker, Z. Margolin, R. J. McCallum, G. J. McCollum, and N. R. Vanier, *J. Am. Chem. Soc.*, **97**, 7006 (1975).
(16) Electron withdrawing groups in the para position of aniline cause the nitrogen pyramid to flatten.[17]
(17) W. J. Hehre, L. Radom, and J. A. Pople, *J. Chem. Soc., Chem. Commun.*, 669 (1972).
(18) A pyramidal site can effectively conjugate with an aromatic ring.[19]
(19) M. J. S. Dewar and P. Rona, *J. Am. Chem. Soc.*, **91**, 2259 (1969).
(20) The question of whether alkyl groups have a significant electron releasing effect and how they interact with electron rich sites is a long-standing one.[21] For a review, see L. S. Levitt and H. F. Widing, *Prog. Phys. Org. Chem.*, **12**, 119 (1976).
(21) R. W. Taft and L. S. Levitt, *J. Org. Chem.*, **42**, 916 (1977); F. G. Bordwell, G. E. Drucker, and G. J. McCollum, *ibid.*, **41**, 2786 (1976); F. G. Bordwell and H. E. Fried, *Tetrahedron Lett.*, 1121 (1977).
(22) A. Streitwieser, Jr., J. R. Murdoch, G. Häfelinger, and C. J. Chang, *J. Am. Chem. Soc.*, **95**, 4248 (1973); A. Streitwieser, Jr., C. J. Chang, and D. M. E. Reuben, *ibid.*, **94**, 5730 (1972); A. Streitwieser, Jr., P. C. Mowery, and W. R. Young, *Tetrahedron Lett.*, 3931 (1971).
(23) Other explanations have been advanced for alkyl group stabilization of carbanions. See C. D. Ritchie and R. E. Uschold, *J. Am. Chem. Soc.*, **89**, 1721 (1967); K. Bowden and A. F. Cockerill, *J. Chem. Soc., B*, 173 (1970).
(24) F. G. Bordwell, W. J. Boyle, Jr., and K. C. Yee, *J. Am. Chem. Soc.*, **92**, 5926 (1970); F. G. Bordwell and W. J. Boyle, Jr., *ibid.*, **97**, 3447 (1975).
(25) A. J. Kresge, *Can. J. Chem.*, **52**, 1897 (1974).
(26) F. G. Bordwell and M. D. Wolfinger, *J. Am. Chem. Soc.*, **93**, 6303 (1971).
(27) A. I. Shatenshtein and H. A. Gvozdeva, *Tetrahedron*, **25**, 2749 (1969).
(28) F. G. Bordwell and W. J. Boyle, Jr., *J. Am. Chem. Soc.*, **93**, 511 (1971); **94**, 3907 (1972); F. G. Bordwell, W. J. Boyle, Jr., J. A. Hautala, and K. C. Yee, *ibid.*, **91**, 4002 (1969).
(29) A. J. Kresge, *J. Am. Chem. Soc.*, **92**, 3210 (1970).
(30) M. Fukuyama, P. W. K. Flanagan, F. T. Williams, Jr., L. Frainier, S. A. Miller, and H. Schechter, *J. Am. Chem. Soc.*, **92**, 4689 (1970).
(31) J. M. Sayer and W. P. Jencks, *J. Am. Chem. Soc.*, **99**, 464 (1977).
(32) M. J. Gregory and T. C. Bruice, *J. Am. Chem. Soc.*, **89**, 2327 (1967).
(33) R. P. Bell, "The Proton in Chemistry", Cornell University Press, Ithaca, N.Y., 1959.
(34) The comparison is based on the assumption that the iminium ion is 200 times more reactive than the corresponding aldehyde.
(35) J. Hine, B. C. Menon, J. H. Jensen, and J. Mulders, *J. Am. Chem. Soc.*, **88**, 3367 (1966); J. Hine, J. Mulders, J. G. Houston, and J. P. Idoux, *J. Org. Chem.*, **32**, 2205 (1967).
(36) M. J. Cook, A. R. Katritzky, and P. Linda, *Adv. Heterocycl. Chem.*, **17**, 256 (1974).
(37) "Handbook of Chemistry and Physics", 46th ed., R. C. Weast, Ed., Chemical Rubber Publishing Co., Cleveland, Ohio, 1966.
(38) R. F. Evans and H. C. Brown, *J. Org. Chem.*, **27**, 1329 (1962).
(39) R. G. Bates, V. E. Bower, and E. R. Smith, *J. Res. Natl. Bur. Stand.*, **56**, 305 (1956).
(40) E. M. Kosower and J. A. Skorcz, *J. Am. Chem. Soc.*, **82**, 2195 (1960).
(41) R. Bates, "Determination of pH. Theory and Practice", Wiley, New York, N.Y., 1964.
(42) A. K. Covington, M. Paabo, R. A. Robinson, and R. G. Bates, *Anal. Chem.*, **40**, 700 (1968).
(43) J. A. Zoltewicz and R. E. Cross, *J. Chem. Soc., Perkin Trans. 2*, 1363 (1974).
(44) A. K. Covington, R. A. Robinson, and R. G. Bates, *J. Phys. Chem.*, **70**, 3820 (1966).
(45) H. S. Harned and B. B. Owen, "The Physical Chemistry of Electrolytic Solutions", 3rd ed., Reinhold, New York, N.Y., 1958, pp 639–643.
(46) G. Graenkel and J. W. Cooper, *J. Am. Chem. Soc.*, **93**, 7228 (1971).